OFFICIAL

IN THE ABSTRACT

Please amend the Abstract as follows:

In the Abstract on line 13, following the phrase "vectors." please insert the following:

-- The present invention further relates to novel vectors characterized by an additional lethal deletion in the E2A early gene region and packaging cell lines which supply the function of the E2A and E4 early gene regions.--

G3

REMARKS

Attorneys for Applicant note their appreciation to Examiner Priebe for the very helpful teleconference on December 7, 1998 and the Examiner's suggested claim language. In addition, Attorneys for Applicant note with appreciation that the Examiner has indicated Claims 39-45, 48-50 and 57 are in condition for allowance.

Claims 37, 38, 46, 47, 52, 54 and 56 have been amended as suggested by the Examiner and to more clearly indicate that which Applicants always intended to be the present invention and further, to limit the issues and place the pending claims in condition for allowance. As requested by the Examiner, an appendix of the claims pending upon entry of this amendment is attached hereto as Exhibit A. The Abstract has been amended as requested by the Examiner to be commensurate in scope with the claimed invention.

1. The Rejections Under 35 U.S.C. § 102 Should Be with Withdrawn

Claims 37, 38, 46, 47, 52, 54 and 56 drawn to a replication-defective recombinant adenovirus are rejected under 35 U.S.C. §102 as anticipated by Gregory et al. U.S. Patent No. 5,670,888 ("Gregory").

Claims 37, 38, 46, 47, 52, 54 and 56 as amended are drawn to recombinant adenoviruses that require at most complementation of the E1 and E4 early gene regions in the absence of the expression of additional adenoviral gene regions in trans. Briefly, the Examiner contends that Gregory anticipates the recombinant adenoviruses and vectors of the present invention which comprise lethal deletions of E1 and E4 gene regions, and optionally E2A. This rejection is in error for the reasons explained below.

The legal test for anticipation under 35 U.S.C. § 102 requires that each and every element of the claimed invention be disclosed in a prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the public in possession of the invention. W.L. Gore Associates v. Galock, Inc., 721 F.2d 1540, 1554 (Fed. Cir. 1983) cert. denied 469 U.S. 857 (1984); In re Donohue, 766 F.2d 351 (Fed. Cir. 1985). Anticipation under 35 U.S.C. § 102 requires identity of invention. Scripps Clinic & Research Fdn. v. Genentech Inc., 927 F.2d 1565 (Fed. Cir. 1991). Anticipation under 35 U.S.C. §102 also requires that the prior art reference places the claimed invention in the possession of the public through an enabling disclosure. Charles v. Miller, 906 F.2d 1574, 15 USPQ 2d 133 (Fed. Cir. 1990).

In this instance, the invention as claimed relates to a replication-defective recombinant adenovirus which requires for replication complementation of genes of both the E1 and E4 early gene regions in the absence of expression of additional adenoviral gene regions in trans. As stated previously, Gregory does not anticipate the recombinant adenoviruses and vectors of the present invention which contain lethal deletions in the E1A and E4 early gene regions and require complementation with E1A and E4 gene regions for rescue in the absence of expression of additional adenovirus genes, or the genomes thereof. The only packaged adenoviral vector described in Gregory is one which must retain the essential region of E4, ORF6, so that complementation with E4 is not required to achieve

rescue of the adenoviral vector. Even as recognized by the Examiner, Gregory does not teach and enable the production of adenoviruses with deletions of the essential regions of E1 and E4 (see Office Action, dated August 31, 1998, page 3, line 18, to page 4, line 2). It simply was not known how to provide the essential functions of both E4 and E1A in a "non-suicidal" packaging cell line.

The essence of the adenoviruses and viral vectors of the present invention is the requirement of complementation of these gene regions without the expression of additional adenoviral gene regions in trans. The deletion of two essential regions, e.g., both the E1 and E4 regions, dramatically minimizes or eliminates the pathogenic effects of direct cytotoxicity to the targeted cells and inflammatory responses in the human body. The resulting virus, however, is replication-defective and requires the E1 and E4 functions in trans in order to replicate.

Prior to the present invention, it was not possible to generate a recombinant adenovirus containing lethal deletions in all of the essential regions of the E1, E2A and E4 gene regions. This is due to the fact that once the DNA encoding the adenoviral genome had been manipulated to contain these deletions, there was no way to provide the toxic gene products encoded by the E1, E2A and E4 gene regions in trans in order to rescue a packaged recombinant adenovirus. This problem was not solved by Gregory, as Gregory does not accomplish nor enable rescue of an adenoviral vector carrying a lethal deletion of the E4 early gene region. In fact a close inspection of the working examples of Gregory reveals that rescue of the PAVs is described in the present tense, thus it is clear that rescue was not achieved, and further, given Gregory's teaching it is doubtful that rescue could actually be accomplished. It was the present invention which provided the methods and the packaging cell line which allows the generation and rescue of a recombinant adenovirus containing lethal deletions of the E1, E2A and E4 early gene regions.

Thus, Gregory does not describe a method of successfully supplying the E4 functions in trans which is necessary to rescue an adenoviral genome containing a lethal deletion or mutation in the E4 early gene region. Rather, Gregory describes a recombinant adenovirus packaged from an adenoviral genome containing a deletion in all of the E4 open reading frames, however, leaving intact the essential E4 open reading frame 6 (ORF6) in order to maintain E4 functions in the virus. However, these deletions of non-essential regions as described in Gregory do not constitute the lethal deletions of E1 and E4 in the replication defective recombinant adenoviruses of the present invention. In fact, the adenoviral vectors as claimed by Gregory require that sufficient E4 sequences are maintained within the viral vectors to promote virus replication.

In summary, Gregory does not describe a recombinant adenovirus, or the rescue of an adenoviral vector, which contains lethal deletions in the E1, E2A and E4 early gene regions, because it was simply not known how to successfully supply the E1, E2A and E4 early gene productsin the absence of additional adenoviral gene products in trans without killing the packaging cell line. It is the instant invention that provides recombinant adenoviruses and vectors containing these lethal mutations, that are successfully rescued and packaged by complementation with E1, E2, and E4 in trans.

Thus, the recombinant adenoviruses and vectors of the present invention are not anticipated by the cited art and, therefore, the Examiner's rejections under 35 U.S.C. § 102 should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. Applicants believe the claims to be in condition for allowance.

Respectfully submitted,

Laura A. Coruzzi by: Jacqueline Bonn Reg No P.43,492

Date January 12, 1999 30,742

Laura A. Coruzzi (Reg. No.)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosure